

Neutrophil function in health and disease

– role of intracellular radicals and galectin-3 as regulators of inflammation

Akademisk avhandling

som för avläggande av medicine doktorsavhandling vid Sahlgrenska akademien vid Göteborgs universitet kommer att offentligen försvaras i föreläsningssalen, våning 3, Guldhedsgatan 10A, Göteborg

Torsdagen den 5 december 2013 kl 13:00

av

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Avhandlingen baseras på följande arbeten:

- I Sundqvist M*, Osla V*, Jacobsson B, Rudin A, Sävman K, and Karlsson A
Cord blood neutrophils display a galectin-3 responsive phenotype accentuated by vaginal delivery
*BMC Pediatrics (2013) 13(1):128 *joint first authorship*
- II Sundqvist M, Wekell P, Osla V, Bylund J, Christenson K, Sävman K, Foell D, Cabral DA, Fasth A, Berg S, Brown KL, and Karlsson A
Increased intracellular oxygen radical production in neutrophils during febrile episodes of periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis syndrome
Arthritis and Rheumatism (2013) 65(11):2971-83
- III Brown KL*, Sundqvist M*, Christenson K, Björnsdóttir H, Osla V, Karlsson A, Dahlgren C, Speert DP, Fasth A, and Bylund J
Elevated mitochondrial reactive oxygen species promote cellular redox imbalance and inflammation in human chronic granulomatous disease
*Submitted Manuscript *joint first authorship*
- IV Sundqvist M, Welin A, Osla V, Nilsson U, Leffler H, Bylund J, and Karlsson A
Type-C self-association of galectin-3 on neutrophil cell surfaces; role of the carbohydrate recognition domain in regulating cell function
In Manuscript



UNIVERSITY OF GOTHENBURG

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– role of intracellular radicals and galectin-3 as regulators of inflammation

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Abstract: The focus for this PhD project has been to investigate neutrophil functions in different (inflammatory) settings with specific focus on phagocyte-derived intracellular reactive oxygen species (ROS) as well as neutrophil interaction with the inflammatory mediator galectin-3.

Neutrophils, the most abundant leukocyte in human blood, have traditionally been viewed upon mainly as professional phagocytes, being able to degrade invading microbes, and thus essential in the defence against infection. However, studies including this thesis, suggest that neutrophils are important players also in sterile inflammatory conditions.

Neutrophils are versatile cells, able to change their appearance and functions in relation to time and localization. Their phenotype can vary from being resting, preactivated/primed or fully activated. The primed neutrophils display increased receptors on their cell surfaces resulting in that they can respond to a variety of stimuli, e.g., the β -galactoside binding lectin galectin-3. ROS produced by neutrophils are primarily thought of as toxic metabolites produced to degrade invading microbes, however, neutrophils can also produce intracellular ROS (icROS) in the absence of microbial uptake and a decrease in these icROS has been correlated to inflammation.

Paper I demonstrates that cord blood neutrophils from term neonates delivered by elective Caesarean section display a primed phenotype, responding to galectin-3, in contrast to adult blood neutrophils. This primed phenotype is accentuated by vaginal delivery. Paper II investigates a pediatric autoinflammatory syndrome, periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA), and demonstrates that three key aspects of neutrophil function, namely apoptosis, priming, and icROS production, are all altered in this disease, most prominently during febrile attacks. Paper III demonstrates that phagocytes from patients with chronic granulomatous disease (CGD), devoid of antimicrobial ROS production, display increased levels of mitochondrial-derived ROS. CGD patients are hyper-susceptible to infections, but also suffer from sterile inflammatory conditions. Paper III suggests that mitochondrial ROS might drive the sterile inflammatory manifestations in CGD. In paper IV, neutrophil interactions with galectin-3 have been studied, and the main results show that a truncated fragment of galectin-3 can inhibit galectin-3 induced activity. Further, a novel type of interaction between galectin-3 and the truncated form, when binding to the cell surface, is presented.

In conclusion, investigation of neutrophils from different settings of health and disease has been utilized to increase our detailed knowledge regarding basic functions in these cells, in addition to providing new information on severe inflammatory syndromes that contribute to the overall understanding of inflammatory diseases.

Keywords: neutrophils, reactive oxygen species, priming, galectin-3, inflammation, PFAPA syndrome, chronic granulomatous disease

ISBN: 978-91-628-8833-6